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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/538,452	06/10/2005	Judith McInally	06275-455US1 100927-1P US	3793

26164 7590 05/05/2008

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EXAMINER	
ANDERSON, REBECCA L	
ART UNIT	PAPER NUMBER
1626	
MAIL DATE	DELIVERY MODE
05/05/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/538,452	MCINALLY ET AL.	
	Examiner	Art Unit	
	REBECCA L. ANDERSON	1626	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 February 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7 and 9-20* is/are pending in the application.

4a) Of the above claim(s) *2,11 and 14-17* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *10 and 13* is/are rejected.

7)☒ Claim(s) *1,3-7,9,10,12,13 and 18-20* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6/10/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-7 and 9-20 are currently pending in the instant application. Claims 2, 11 and 14-17 are withdrawn from consideration as being for non-elected subject matter. Claims 1, 3-7, 9, 10, 12, 13 and 18-20 are objected to as containing non-elected subject matter. Claims 10 and 13 are rejected.

Election/Restrictions

Applicant's election without traverse of Group I, including claims 10 and 13 in the reply filed on 8 February 2008 is acknowledged. Additionally, claims 1-7, 9, 12 and 15-20 are included in the search and examination of Group I. Applicant also elected the species of Example 1.

As per MPEP 803.02, the examiner will determine whether the entire scope of the claims is patentable. Applicants' elected species is not allowable. Therefore, according to MPEP 803.02:

> Following election, the Markush-type claim will be examined fully with respect to the elected species and further to the extent necessary to determine patentability. If the Markush-type claim is not allowable **, the provisional election will be given effect and examination will be limited to the Markush-type claim and claims to the elected species, with claims drawn to species patentably distinct from the elected species held withdrawn from further consideration.
> the elected species shall be rejected, and claims to the nonelected species will be held withdrawn from further consideration.

As the elected species has been found not allowable, the Markush-type claims have been rejected and claims to the nonelected invention held withdrawn from further consideration.

Claims 1, 3-7, 9, 10, 12, 13 and 18-20 **have been examined to the extent that they are readable on the elected embodiment, the elected species of Example 1.** Since the elected species is not allowable, subject matter not embraced by the elected

embodiment is therefore withdrawn from further consideration. It has been determined that the entire scope claimed is not patentable.

The requirement is still deemed proper and is therefore made FINAL.

Claim Objections

Claims 1, 3-7, 9, 10, 12, 13 and 18-20 are objected to as containing non-elected subject matter. Claims 1, 3-7, 10, 12, 13 and 18-20 presented drawn solely to the elected embodiment would overcome this objection.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 10 and 13 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

As stated in the MPEP 2164.01 (a), "There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue."

In *In re Wands*, 8 USPQ2d 1400 (1988), factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have need described. They are:

1. the nature of the invention,
2. the state of the prior art,
3. the predictability or lack thereof in the art,
4. the amount of direction or guidance present,
5. the presence or absence of working examples,
6. the breadth of the claims,
7. the quantity of experimentation needed, and
8. the level of the skill in the art.

In the instant case:

The nature of the invention

The nature of the invention of claims 10 and 13 is a method for producing inhibition of a cysteine protease in a mammal in need of such treatment.

The State of the prior art and the predictability or lack thereof in the art

The state of the prior art, pharmacology, involves screening in vitro and in vivo to determine whether and which amongst a given genus of compounds exhibits the desired pharmacological activities, in this case inhibition of a cysteine protease. It is noted that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. In re Fisher, 427 F.2d 833, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute.

According to Vasiljeva et al., there is a multitude of cysteine proteases, such as cathepsins B, C, F, H, K, L, O, S, V, W, X, etc., page 387. According to Vasiljeva, et

al., cathepsin S, the only cysteine protease discussed in any detail in applicants' specification, is known to play a role in the following biological functions of cysteine cathepsine knock-out mice: 1) Immune defect: impaired invariant chain degradation in antigen presenting cells; 2) Diminished susceptibility to an experimentally elicited autoimmunity, collagen-induced arthritis; 3) Reduced atherosclerosis in atherosclerosis-prone LDL receptor-deficient mice; 4) Reduced wound-healing—associated neovascularization; 5) Decreased plaque size and the incidence of acute plaque rupture in animal model of spontaneous plaque destabilization; 6) Resistant to the development of experimental autoimmune myasthenia gravis; and 7) Reduced angiogenesis and growth of solid tumours in RIP1-Tag2 transgenic tumour model. Despite the role of cathepsin S in the aforementioned biological functions, there is not enough evidence as of 2007 to make a claim that applicants' elected embodiment is capable of treating a mammal with the inhibition of any cysteine protease. For instance, cathepsin S could be said to play a role in the proteolytic events during tumour progression. *Id.* at 390. However, there is no evidence supporting cathepsin S's role in the treatment of cancer. Rather, at this point, cathepsin S is merely a relevant drug target for the treatment of cancer. Despite the fact cathepsin S is known to have a role in many biological functions, it cannot be induced from this knowledge that every disease in which cathepsin S is known to play a role can be treated by a given genus of compounds inhibiting any cysteain protease, including cathepsin S. The Examiner can find no evidence in the art supporting Applicant's **claims 10 and 13**. That is, at the time of filing

of the instant disclosure, there is no evidence supporting the elected embodiment can inhibit any cysteine protease in a mammal in need of such treatment.

In fact, in a 2004 review on cathepsin S inhibitors, Leroy, et al. note certain reported data which indicates

"some [cathepsin S] inhibitors are active *in vivo* after oral administration...This clearly is a progress towards the successful development of cathepsin S inhibitors as potential drugs...At the time of this review, none of these compounds have been reported to reach the clinic. The results of such trials will tell if cathepsin S inhibitors can fulfill their potential seen in animal models and deliver new approaches for the treatment of rheumatoid arthritis, asthma, COPD and atherosclerosis."

It could be concluded, then, that as of 2004, the level of skill in the art supported cathepsin S inhibitors as potential drug targets requiring further development. There is no conclusive evidence presented either in the literature or the Specification which would lead a person of ordinary skill in the art to conclude that applicants' elected embodiment can inhibit any cysteine protease in a mammal in need of such treatment.

Lastly, Palermo et al. discloses that in regards to cysteine cathepsin inhibitors, only a few of the small-molecule inhibtors have so far been tested in animal models of cancer and that the importance of preclinical evaluation is underscored by the finding that some inhibitors that show significant potency in initial in vitro validation assays have diminished efficacy and increased off-target effects in vivo, page 25. Palermo et al. states that this may arise because cell-based culture systems do not fully recapitulate the complex tumor microenvironment in which cysteine cathepsins function in vivo. Lastly Palermo et al. states that it will be essential to address the general importance of cysteine cathepsins in cancer progression and metastasis in a broad range of additional

transgenic and "knock-in" preclinical models of cancer, before advancing to the clinic with these inhibitors. An additional concern is that when targeting a family of enzymes such as the cysteine cathepsins is whether there are tumor-suppressing cysteine cathepsins in addition to the tumor-promoting family members.

Hence, in the absence of a showing of correlation between the inhibition of any cysteine protease, the elected embodiment and the in vivo use in a mammal in need of such treatment, one of skill in the art is unable to fully predict possible results from the administration of the compound of the claims due to the unpredictability of the role of the inhibition of any cysteine protease. Furthermore, in the absence of any examples as to how to determine what mammal would be in need of such treatment and in the absence of any in vitro or in vivo data for the multitude of cysteine proteases, one of skill in the art is unable to fully predict possible results from the administration of the compound of the elected embodiment.

The nature of pharmaceutical arts is that it involves screening *in vitro* and *in vivo* to determine which compounds exhibit the desired pharmacological activities. There is no absolute predictability even in view of the seemingly high level of skill in the art. The existence of these obstacles establishes that the contemporary knowledge in the art would prevent one of ordinary skill in the art from accepting any therapeutic regimen on its face.

The amount of direction or guidance present and the presence or absence of working examples

While applicants' claims are to the inhibition of any cysteine protease, the only direction or guidance in the specification is the broad statement that the compounds of the invention are reversible inhibitors of cysteine proteases S, K, F, L and B on page 1, the discussion of cathepsin S on page 1 and direction on how to measure cathepsin S activity in vitro with no activity provided for any compound. There is no in vivo date for cathepsin S, nor is there any in vitro or in vivo data for any other cysteine protease such as K, F, L and B. There is also no data for the multitude of other cysteine proteases such as cathepsins C, J, I, H, O, V, W or X which are included in the claims to the inhibition of any cysteine protease.

The breadth of the claims

The breadth of the claims includes the inhibition of any cysteine protease, such as S, K, F, L, B, C, J, I, H, O, V, W or X in a mammal in need of such treatment.

The quantity of experimentation needed and the level of the skill in the art

The quantity of experimentation needed is undue. While the level of skill in the art is high, it would require undue experimentation to determine what cysteine protease can be inhibited by the compounds of the instant claims. Due to the unpredictability in the pharmaceutical art, it is noted that each embodiment of the invention is required to be individually assessed for physiological activity by in vitro and in vivo screening to determine which compounds exhibit the desired pharmacological activity and which diseases would benefit from this activity, i.e. what mammal would be in need of such treatment.

After pinpointing which compounds exhibit the desired effect, a determination must be made as to whether said effect is useful in a mammal in need of such treatment. Such a determination requires more screening in vitro and in vivo prior to any real conclusions can be made as to whether compound X, exhibiting X desired effect, can be used to treat a mammal in need of treatment. Much of the screening has, by now, become routine in the art. The pharmaceutical industry is well equipped to make determinations of a given compound's ability to function as intended. However, despite the exceedingly high level of skill possessed by the average pharmacological artisan, there is no absolute predictability. Moreover, it cannot be said that such determinations are predictable, *per se.* Numerous assays must be run, numerous *in vitro* studies must be run, and numerous *in vivo* studies must be run prior to a determination as to whether a given compound can treat a mammal in need of such treatment. Additionally, the only data provided in Applicants' specification is how to determine in vitro activity for cathepsin S with no activity provided for any compound. It would require undue experimentation to determine whether the compounds of the invention would be able to inhibit any other cysteine protease. In addition, it would require undue experimentation to determine what mammals would be in need of treatment by the inhibition of any cysteine protease when no in vivo data is present in the specification and no correlation data presented correlating the in vitro data for the cathespin S activity to the treatment of any mammal in vivo by inhibiting any cysteine protease.

Thus, the specification fails to provide sufficient support of the broad intended use of the elected embodiment for the inhibition of any cysteine protease in a mammal in need of such treatment.

Genentech Inc. v. Novo Nordisk A/S (CA FC) 42 USPQ2d 1001 , states that " a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable".

Therefore, in view of the Wands factors and In re Fisher (CCPA 1970) discussed above, to practice the claimed invention herein, a person of skill in the art would have to engage in undue experimentation with no assurance of success.

Conclusion

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Rebecca L. Anderson whose telephone number is (571) 272-0696. Mrs. Anderson can normally be reached Monday through Friday from 6:00am until 2:30pm.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Mr. Joseph K. McKane, can be reached at (571) 272-0699.

The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Rebecca Anderson/
Primary Examiner, AU 1626

1 May 2008

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